Robust Summary - Group 1: High Butadiene C4

Acute Toxicity

Test Substance	
Remarks	Butadiene Concentrate, CAS# 68955-28-2 Gases (petroleum) light steam-cracked, butadiene conc. Approximately 45% 1,3-butadiene, 20% butanes, and 30% butenes.
Method	
Method/guideline followed	OECD 402.
Type (test type)	Acute inhalation.
GLP	Yes.
Year	1982.
Species/Strain	Rat/Fischer 344.
Sex	Males and females.
No. of animals per sex per dose	5/sex.
Vehicle	Not applicable.
Route of administration	Inhalation (gas).
Test Conditions	A group of ten rats (age: 12 weeks, weight: 143-234 grams) were exposed to 5300 mg/m3 (2331 ppm) of the test substance in air for four hours. Analytical chamber concentrations were determined by gas chromatography every 15 minutes during the exposure; a single particle size sample was taken to show the absence of aerosol. Body weights were recorded prior to exposure and 7 and 14 days post-exposure. Individual clinical observations were recorded pre-exposure and daily for 14 days post-exposure. The rats were sacrificed on the fourteenth day and a gross necropsy performed.
Results	
LC50	Rat LC50 (4 hour) = >5300 mg/m3 (2331 ppm).
Remarks	Observations noted following exposure were two male rats with respiratory sounds/wheezing or hyperexcitability and one female with minimal porphyrin around the eyes. All rats were normal from Days 2-14. No significant necropsy findings were reported, except one female with an ovary filled with red fluid. Body weight gains appeared normal.
Conclusions	
(study author)	No mortality or significant adverse effects were observed in rats exposed to 5300 mg/m3 (2331 ppm) of the test substance.
Data Quality	
Reliability	Reliable without restrictions. Guideline study.
References	Gulf Oil Chemicals Company (1982). Acute LC50 Inhalation Toxicity Test in Rats with Butadiene Feedstock. Unpublished report (Project #82-060).
Other	Robust Summary prepared by ExxonMobil Biomedical Sciences, Inc.
Last changed	19-Oct-99

Robust Summary - Group 1: High Butadiene C4

Acute Toxicity

Test Substance	1,3-butadiene CAS# 106-99-0
Method	
Method/guideline followed	Other.
Type (test type)	Acute inhalation.
GLP	Pre-GLP.
Year	1969.
Species/Strain	Rat and mouse (strains not specified).
Sex	Not specified.
No. of animals per sex per dose	Not specified.
Vehicle	Not applicable.
Route of administration	Inhalation (gas).
Test Conditions	Age, number, and sex of test animals not specified. Number of groups and exposure concentrations not specified. Dynamic flow exposure system; no description of exposure chambers or conditions. Rats exposed four hours; mice exposed two hours. No post-exposure observation period - mortality study only. Exposure concentrations "controlled" by gas chromatography.
Results	
LC50 with confidence limits	Rat LC50 (4 hour) = 285 mg/L (219-370 mg/L $p \leq 0.05$) Mouse LC50 (2 hour) = 270 mg/L (251-290 mg/L $p \leq 0.05$)
Remarks	No clinical observations or necropsy findings reported. Objective of study was to determine hydrocarbon concentrations in various tissues at lethal exposure concentrations.
Conclusions	
(study author)	LC50 value reported to be 285 mg/L (129,000 ppm) in rats, 270 mg/L (122,000 ppm) in mice.
Data Quality	
Reliability	Not assignable. Lethality study only; insufficient experimental detail to assess quality.
References	Shugaev, B.B. (1969) Concentrations of Hydrocarbons in Tissues as a Measure of Toxicity. Arch. Environ. Health 18:878-882.
Other	Robust Summary Prepared by ExxonMobil Biomedical Sciences, Inc.
Last changed	13-Oct-99

Robust Summary - Group 1: High Butadiene C4

Acute Toxicity

Test Substance	Butadiene Concentrate, CAS# 68955-28-2 Gases (petroleum) light steam-cracked, butadiene conc. Approximately 67% 1,3-butadiene, 30% butenes, 2% 1,2-butadiene
Method	
Method/guideline followed	Other.
Type (test type)	Irritation screen in rabbits.
GLP	Yes.
Year	1985.
Species/Strain	Rabbit (New Zealand White).
Sex	1 male, 1 female.
Vehicle	Not applicable.
Route of administration	Eye and skin.
Remarks For Test Conditions	Two young adult rabbits were evaluated for eye and skin irritation. The test substance was dispensed immediately prior to dosing into a flask packed in dry ice. On the first treatment day, 0.1mL of the test substance was instilled into one eye of each rabbit. Irritation was scored at 24, 48, and 72 hours. The untreated eye served as the control. Twenty-four hours after treatment of the eye, 0.1mL of the test substance was applied to the skin of the rabbits and occluded with a rubber dam. The test sites were evaluated 1, 3, and 7 days after dosing.
Results	
Remarks	The eye irritation scores were 0 at all observation intervals. The treated skin sites were virtually free of irritation at all observation intervals.
Conclusions	
(study author)	The test substance is estimated not to be irritating to the eye or skin.
Data Quality	
Reliability	Reliable with restrictions. Screening study.
References	Mobil Environmental and Health Sciences Laboratory (1985). Irritation Screen of Butadiene Concentrate in Albino Rabbits, Unpublished report (Study No. 41652).
Other	Robust Summary prepared by ExxonMobil Biomedical Sciences, Inc.
Last changed	24-Oct-99

Robust Summary - Group 1: High Butadiene C4

Genetic Toxicity - in Vitro

Test Substance	
Test substance	1,3-butadiene CAS# 106-99-0
Method	
Method/guideline followed	No data.
Type	Reverse mutation assay (Ames *Salmonella* test).
System of testing	Bacterial.
GLP	No data.
Year	1990.
Species/Strain	Salmonella typhimurium/TA97, TA98, TA100, TA1535.
Metabolic activation	With and without.
Species and cell type	Rat, mouse, and human liver S9 fraction.
Quantity	0.8 and 4.0 mg protein/plate.
Induced or not induced	Arochlor 1254-induced and uninduced rat, mouse, and human S9.
Concentrations tested	0, 30, 40, 50, and 60% butadiene in air.
Statistical Methods	Not specified.
Remarks for Test Conditions	Concentrations of butadiene gas were metered into specially constructed treatment chambers holding the agar plates overlaid with the bacteria and activation system. Actual gas concentrations were determined by gas chromatography before and after the 48 hour exposure period. Different treatment chambers were used for each activation system and for the non-activated treatment. S9 preparations were made according to the procedure of Ames et al. (1975).
Results	1,3-Butadiene (BD) induced revertants only in strain TA1535. Mouse S9 showed slightly higher activity than the uninduced rat or human S9 at 30% BD in air. At concentrations greater than 30%, the number of revertants decreased in the presence of rat or human S9. Results from the human S9-activated treatments did not differ substantially from those of the non-activated treatments. Arochlor 1254-induced rat S9 gave similar results as mouse S9 (uninduced). Since the response was weak, the S9 concentration was increased from 0.8 mg/plate to 4.0 mg/plate. Increasing the concentration of Arochlor 1254-induced rat S9 had no effect on the number of revertants; slightly more revertants were observed using 4.0 than 0.8 mg/plate of uninduced rat S9.
Conclusions	
(study author)	*Salmonella typhimurium* reverse gene mutation (Ames) tests of 1,3-butadiene using strains TA1535, TA97, TA98, and TA100 and employing rat, mouse, and human liver S9 metabolic systems were barely 2-fold above background only in strain TA1535 at 30% butadiene in air with induced and uninduced rat S9 and mouse S9 (uninduced). In general, 1,3- butadiene was a weak *in vitro* genotoxin.
Data Quality	
Reliabilities	Reliable without restrictions. Comparable to guideline study.
Reference	Arce G.T., Vincent D.R., Cunningham M..J, Choy W.N., and Sarrif A.M. (1990). In vitro and in vivo genotoxicity of 1,3-butadiene and metabolites. Environ. Health Perspect. 86:75-8.
Other	Robust Summary Prepared by ExxonMobil Biomedical Sciences, Inc.
Last changed	18-Oct-99

Robust Summary - Group 1: High Butadiene C4

Genetic Toxicity - in Vitro

Test Substance	
Test substance	Butadiene Concentrate, CAS# 68955-28-2. Gases (petroleum) light steam-cracked, butadiene conc. Approximately 45% 1,3-butadiene, 20% butanes, and 30% butenes.
Method	
Method/guideline followed	OECD 482.
Type	Unscheduled DNA Synthesis (UDS).
System of testing	Primary hepatocytes derived from Fischer 344 rats.
GLP	Yes.
Year	1984.
Metabolic activation	No.
Concentrations tested	0, 1000, 5000, 10000, and 20000 ppm.
Control groups and treatment	Negative = air only; positive = 2-acetylaminofluorene (0.2ug/mL).
Statistical Methods	Group means and standard deviations for number of viable cells and nuclear grain counts. The test substance was considered positive if the mean nuclear grain count exceeded the negative control by at least 6 grains per nucleus and the negative control did not exceed 5.
Remarks for Test Conditions	Primary hepatocytes were derived from freshly perfused rat liver (1 male, 10 weeks age, 226 grams body weight). Cultures were seeded with approximately 10^5 cells/mL on Day 1. Three cultures per group were exposed to ^{3}H-thymidine and the test substance for 18-20 hours. The culture flasks were placed in sealed dessicator jars for the exposure period, and the test substance added by injection via a 50cc syringe. Cells growing on coverslips were fixed on Day 2. On Day 3 the slides were dipped in autoradiograph emulsion and stored in the dark at 2-8^{o}C. The autoradiographs were developed and stained on Day 21.
Results	A separate range-finding study was conducted to establish levels of cytotoxicity based on relative cell viability. The test substance was toxic to primary hepatocytes at 10000 ppm where 64% relative viability was observed following 18 hour exposure. At 20000 ppm, the relative viability was 57%. In the UDS study, both positive and negative control groups gave expected responses. A weak positive response was observed at 20000 ppm (7.74 nuclear grain counts vs. 1.24 in the air control vs. 107.13 in the positive control). The 1000, 5000, and 10000 ppm groups were also slightly increased (4.29-5.14) from the air control but less than the criteria for a significant response.
Conclusions	
(study author)	Cytotoxicity was observed at 10000 ppm. Increased unscheduled DNA synthesis was observed at 20000 ppm.
Data Quality	
Reliabilities	Reliable without restrictions. Guideline study.
Reference	Gulf Oil Chemicals Company (1984). Hepatocyte Primary Culture/DNA Repair Test of Butadiene Feedstock, Unpublished report (Project# 2073).
Other	Robust Summary Prepared by ExxonMobil Biomedical Sciences, Inc.
L*ast changed*	18-Oct-99

Robust Summary - Group 1: High Butadiene C4

Genetic Toxicity - in Vitro

Test Substance	
Test substance	Butadiene Concentrate, CAS# 68955-28-2 Gases (petroleum) light steam-cracked, butadiene conc. Approximately 45% 1,3-butadiene, 20% butanes, and 30% butenes.
Method	
Method/guideline followed	Other.
Type	Mammalian cell transformation test.
System of testing	BALB/3T3-A31-1-1 cells.
GLP	Yes.
Year	1983.
Metabolic activation	No.
Concentrations tested	0, 1000, 5000, 10000, and 20000 ppm.
Control groups and treatment	Negative = air only; positive = 3-methylcholanthrene (1.0 ug/mL).
Statistical Methods	Group means and standard deviations for number of viable cells, cloning efficiency, and transformed foci per culture. The test substance was considered positive if there was a two-fold increase in foci compared to the negative control group.
Remarks for Test Conditions	Each treatment group consisted of 12 flask cultures for cell transformation seeded with 10000 cells and 2 plate cultures for cloning efficiency with 250 cells. The cultures were placed in sealed dessicator jars and exposed to the test substance for two days. The test substance was added to the jars by injection via a 50cc syringe and samples of the exposure atmosphere were analyzed by gas chromatography. The mediums were changed on Day 4 and then weekly. Plate cultures were fixed and stained on Day 8 and flask cultures on Day 29. Foci in transformation cultures were counted and examined microscopically to determine type.
Results	Cloning efficiency was used as a measure of toxicity under culture conditions. Toxicity was observed at 5000 ppm where a relative cloning efficiency of 53.8% was observed. The negative and positive control gave expected responses for transformation. The response for the test substance was not increased from the negative control group at any level tested.
Conclusions	
(study author)	The test substance was negative for cell transformation.
Data Quality	
Reliabilities	Reliable without restrictions. Comparable to draft OECD guideline.
Reference	Gulf Oil Chemicals Company (1983). BALB/3T3 Transformation Test Using Butadiene Feedstock, Unpublished report (Project# 2074).
Other	Robust Summary Prepared by ExxonMobil Biomedical Sciences, Inc.
Last changed	18-Oct-99

Robust Summary - Group 1: High Butadiene C4

Genetic Toxicity - in Vitro

Test Substance	
Remarks	Butadiene Concentrate, CAS# 68955-28-2 Gases (petroleum) light steam-cracked, butadiene conc. Approximately 67% 1,3-butadiene, 30% butenes, 2% 1,2-butadiene.
Method	
Method/guideline followed	No data.
Type	Reverse mutation assay (Ames *Salmonella* test).
System of testing	Bacterial.
GLP	Yes.
Year	1985.
Species/Strain	Salmonella typhimurium/ TA98, TA100, TA1535, TA1537, TA1538.
Metabolic activation	With and without.
Species and cell type	Rat liver S9 fraction.
Quantity	0.6 mL.
Induced or not induced	Arochlor 1254-induced.
Concentrations tested	25, 50, 75, or 100 uL.
Statistical Methods	The test substance was considered mutagenic if it produced a dose-related two-fold increase in mean revertant value compared to the negative control.
Remarks for Test Conditions	The test substance was stored in a dry ice/ethanol slurry to prevent loss of volatile components and dosed by microdispenser into sterile septa-capped culture tubes. Sodium phophate buffer or S-9/bacteria mix was injected through the septa into the tubes containing the test substance and pre-incubated for 20 minutes at 37^{o}C. After the pre-incubation period, the contents of the tubes were overlayed on agar and incubated for 48 hours at 37^{o}C. Revertant colonies were counted by automatic colony counter. Positive control chemicals were: 2.0 ug 2-aminoanthracene, 15.0 ug 9-aminoacridine, 20.0 ug 2-nitrofluorene, and 5.0 ug N-methyl-N-nitro-N-nitrosoguanidine, in 50 uL DMSO per plate.
Results	A preliminary toxicity/initial mutagenicity assay was conducted over a range of 10 to 500 uL per plate in two strains (TA100 and TA1537) with and without S-9. Toxicity was exhibited at $\geq$75uL in TA100, and $\geq$100uL in TA1537. Some inconsistencies in toxicity with increasing dose level were noted that were attributed to the volatility of the test substance. Based on the toxicity data, the test substance was tested in the pre-incubation mutagenicity assay at volumes of 25, 50, 75, and 100 uL per plate. None of the five strains with or without induced rat liver S-9 exhibited reversion frequencies substantially different from spontaneous controls in this assay.
Conclusions	
(study author)	The test substance was not considered a mutagen with or without metabolic activation in this test system.
Data Quality	
Reliabilities	Reliable without restrictions. Comparable to guideline study.
Reference	Mobil Environmental and Health Sciences Laboratory (1985). An Ames Salmonella/Mammalian Microsome Mutagenesis Assay For Determination of Potential Mutagenicity of Butadiene Concentrate, Unpublished report (Study No. 41653).

Other	Robust Summary Prepared by ExxonMobil Biomedical Sciences, Inc.
Last changed	24-Oct-99

Robust Summary - Group 1: High Butadiene C4

Genetic Toxicity - in Vitro

Test Substance	
Remarks	Butadiene Concentrate, CAS# 68955-28-2 Gases (petroleum) light steam-cracked, butadiene conc. Approximately 67% 1,3-butadiene, 30% butenes, 2% 1,2-butadiene.
Method	
Method/guideline followed	Other.
Type	Mouse lymphoma mutagenesis assay.
System of testing	Mammalian cell.
GLP	Yes.
Year	1985.
Species/Strain	Mouse lymphoma cells/ L5178Y (TK+/-; subclone 3.7.2C).
Metabolic activation	With and without.
Species and cell type	Rat liver S9 fraction.
Quantity	4.0 mL.
Induced or not induced	Arochlor 1242/1254-induced.
Concentrations tested	Nonactivated assays: 10.0, 12.5, 15.0, 17.5, 20.0, 22.5, 25.0, 27.5, 30.0, 35.0 40.0, or 45.0 uL/mL media. S-9 activated assays: 2.5, 5.0, 7.5, 10.0, 12.5, 15.0, 17.5, 20.0, 22.5, or 25.0 uL/mL.
Statistical Methods	The test substance was considered mutagenic if it produced a dose-related or toxicity-related two-fold increase in average mutant frequency compared to the negative controls, at concentrations exhibiting acceptable total growths (10% or greater).
Remarks for Test Conditions	The positive control chemical for the S-9 activated assays was 7, 12-dimethylbenz[a]anthracene (DMBA) at 2.5 and 5.0 ug/mL, and ethylmethane sulfonate (EMS) for the nonactivated assays at 0.5 and 1.0 uL/mL. An initial toxicity assay was performed with and without activation at concentrations ranging from 10 to 100 uL/mL. The dosing regimen for the mutagenesis assay was designed to produce 10-90% lethality. Six mLs of cell suspension (10^6 cells/mL) were exposed for 3 hours to the test or positive control substances. An expression period of 2 days followed with determinations of cell population densities and growth. Cultures selected for mutant analysis and cloning efficiencies were incubated for 10-12 days.
Results	Without activation, mutant frequencies and total number of mutants were significantly increased at the two highest concentrations (20.0 and 22.5 uL/mL). Although total growth was very low (5.1% and 5.5%), these levels were considered mutagenic since there was no reduction in cloning efficiency. There were no significant differences in mutant frequency for the S-9 activated cultures.
Conclusions	
(study author)	The test substance induced a significant increase in mutant frequency of mouse lymphoma cells without metabolic activation, but was evaluated as non-mutagenic in the presence of S-9 activation.
Data Quality	
Reliabilities	Reliable without restrictions. Comparable to guideline study.

Reference	Mobil Environmental and Health Sciences Laboratory (1985). Evaluation of the Mutagenic Potential of Butadiene Concentrate in the Mouse Lyphoma (L5178Y/TK+/-) Mutagenesis Assay, Unpublished report (Study No. 41654).
Other *Last changed*	Robust Summary Prepared by ExxonMobil Biomedical Sciences, Inc. 24-Oct-99

Robust Summary - Group 1: High Butadiene C4

Genetic Toxicity - in Vivo

Test Substance	
Remarks	1,3-butadiene CAS# 106-99-0
Method	
Method/guideline followed	Other.
Type	Mammalian erythrocyte micronucleus assay.
GLP	No data.
Year	1994.
Species	Rat and mouse.
Strain	Rat: Wistar. Mouse: CB6F1
Sex	Rat: Male. Mouse: Female.
Route of administration	Inhalation (gas).
Doses/concentration levels	0, 50, 200, or 500 ppm.
Exposure period	6 hours/day for 5 days.
Statistical methods	Student's two-tailed t-test for differences between groups.
Remarks for Test Conditions.	Twenty female CB6F1 mice (approximately 25g, 8-10 weeks old) and ten male Wistar rats (300-350g, 10 weeks old) per group were exposed for 5 days, 6 h/day 0, 50, 200, or 500 ppm of 1,3-butadiene (BD) by inhalation. An additional high concentration group of mice was exposed to 1300 ppm. Exposure concentrations were monitored by infrared spectroscopy (rats) and gas chromatography (mice). The animals were sacrificed 1 day after the last exposure and smears of blood and bone marrow erythrocytes were prepared and stained.
Results	In the rats, no effects on micronuclei frequencies were observed either in the peripheral blood or bone marrow at all exposure levels. A slight toxic effect in rat bone marrow cells (decreased polychromatic/normochromatic ratio) was observed at the 500 ppm level. In the mice, a clear dose-dependent increase in micronuclei frequency was observed in both blood and bone marrow cells at all exposure levels tested.
Conclusions	
(study author)	1,3-butadiene was active in inducing micronuclei in peripheral blood and bone marrow erythrocytes in mice at levels $\geq$50 ppm, but not in rats. The genotoxic effects observed in this study parallel the species differences observed in cancer studies.
Data Quality	
Reliabilities	Reliable without restrictions. Comparable to guideline study.
References	Autio, K., Renzi, L., Catalan, J., Albrecht, O.E., and Sorsa, M. (1994). Induction of Micronuclei in Peripheral Blood and Bone Marrow Erythrocytes of Rats and Mice Exposed to 1,3-Butadiene by Inhalation. Mut. Res. 309:315-320.
Other	Robust Summary Prepared by ExxonMobil Biomedical Sciences, Inc.
Last changed	25-Oct-99

Robust Summary - Group 1: High Butadiene C4

Genetic Toxicity - in vivo

Test Substance	
Remarks	Butadiene Concentrate, CAS# 68955-28-2 Gases (petroleum) light steam-cracked, butadiene conc. Approximately 45% 1,3-butadiene, 20% butanes, and 30% butenes.
Method	
Method/guideline followed	OECD 474.
Type	Mammalian erythrocyte micronucleus test.
GLP	Yes.
Year	1984.
Species	Mouse.
Strain	Crl:CD-1 BR Swiss.
Sex	Male and female.
Route of administration	Inhalation (gas).
Doses/concentration levels	10780, 20671, 35430 ppm.
Exposure period	2 hours/day for 2 consecutive days.
No. of animals per dose	10/sex/group.
Control groups and treatment	10/sex negative (air) control; 5/sex positive control (cyclophosphamide, 75 mg/kg intraperitoneal injection).
Statistical methods	Group mean body weights, total polychromatic erythrocytes (PCEs), normochromatic erythrocytes (NORMs), PCEs with micronuclei, and NORMs with micronuclei were compared by t-test ($p<0.05$ = positive).
Remarks for Test Conditions.	Mice were 11 weeks old and 25-42 grams weight at study initiation. Test and control substances were administered on Days 1 and 2. Exposure concentrations determined by gas chromatography. Animals were observed daily and body weights were recorded on Days 1, 3, and 4. Five mice/sex/group were sacrificed on Days 3 and 4 and bone marrow smears prepared; positive controls (5/sex) were sacrificed on Day 3 only.
Results	No mice died during the study; the only clinical observations were an apparent unconsciousness during exposure. There were no significant body weight differences. The negative and positive control groups produced negative and positive resulats, respectively. Mice in the exposed groups showed increased micronuclei formation at all levels in both sexes. Females were statistically increased from control at all levels on Day 3 and at 20671 ppm and 35430 ppm on Day 4; males were significantly increased only at 35430 ppm on both days. There was no significant change in the PCE/NORM ratio in any group.
Conclusions	
(study author)	The test material produced an increased frequency of micronucleated erythrocytes in the bone marrow of mice at all levels tested.
Data Quality	
Reliabilities	Reliable without restrictions. Guideline study.
References	Gulf Oil Chemicals Company (1984). Micronucleus Test in Mouse Bone Marrow: Butadiene Feedstock Administered by Inhalation For 2 Hours/Day For 2 Days, Unpublished report (Project #2014).
Other	Robust Summary Prepared by ExxonMobil Biomedical Sciences, Inc.
Last changed	13-Oct-99

Robust Summary - Group 1: High Butadiene C4

Repeated Dose Toxicity

Test Substance	
Remarks	1,3-butadiene, CAS# 106-99-0 Rubber grade, containing 0.02% t-butyl catechol; purity ≥98.94%.
Method	
Method/guideline followed	Other.
Test type	14-week inhalation study.
GLP	Yes.
Year	1977.
Species	Mouse.
Strain	B6C3F1.
Route of administration	Inhalation (gas).
Duration of test	14 weeks.
Doses/concentration levels	0, 625, 1250, 2500, 5000, or 8000 ppm.
Sex	10 male, 10 female per group.
Exposure period	6 hours/day.
Frequency of treatment	5 days/week, total of 63 or 64 exposures.
Control group and treatment	10 male, 10 female, air-only exposed.
Post exposure observation period	Not applicable.
Statistical methods	Group means and standard deviations calculated for body weights.
Test Conditions	Groups of 10 mice/sex /group (4-5 weeks age at study initiation) were exposed to various levels of 1,3-butadiene for 6 hrs/day, 5 days/week for 14 weeks (64 exposures). Because four male mice in the high exposure group died by day 4, another 2 groups of 10 male mice each were restarted (control and 8000 ppm). Mice were observed once daily for morbidity and mortality; moribund animals were sacrificed. Body weights were recorded weekly. At the end of the 95 or 93-day (restart) studies, surviving mice were sacrificed. Necropsies were performed and tissues preserved. Histopathologic examinations were performed on all controls, high exposure (8000 ppm), and early deaths.
Results	
NOAEL (NOEL)	1250 ppm.
LOAEL (LOEL)	2500 ppm, based on reduced body weight gains.
Remarks	Six of ten males and 1/10 females exposed at 8000 ppm, 6/10 males and 1/10 females at 5000 ppm, and 1/10 males at 2500 or 1250 ppm died prior to study termination or were sacrificed in a moribund condition. Body weight gains were decreased in males at 2500, 5000, and 8000 ppm, and at 5000 and 8000 ppm in the females. No exposure-related histopathologic effects were observed in the high (8000 ppm) group.
Conclusions	Based on the results of this study, exposure levels of 625 and 1250 ppm were selected for a 2-year carcinogenicity study in mice based on reduced body weight gains and mortality in higher exposure groups.
Data Quality	
Reliabilities	Reliable with restrictions. Acceptable, well-documented study report but deficient by current guidelines. No organ weights, hematology or clinical chemistry evaluations were performed.

References	National Toxicology Program, Toxicology and Carcinogenesis Studies of 1,3-Butadiene (CAS No. 106-99-0) in B6C3F1 Mice (Inhalation Studies), NTP Technical Report Series No. 288, NIH Publication 84-2544 (1984).
Other Last changed	Robust Summary Prepared by ExxonMobil Biomedical Sciences, Inc. 8-Dec-99

Robust Summary - Group 1: High Butadiene C4

Repeated Dose Toxicity

Test Substance	
Remarks	1,3-butadiene, CAS# 106-99-0 Purity >99.2%, containing 120 ppm t-butyl catechol.
Method	
Method/guideline followed	Other.
Test type	13-week inhalation study.
GLP	No data.
Year	1977.
Species	Rat.
Strain	CD (Sprague-Dawley).
Route of administration	Inhalation (gas).
Duration of test	14 weeks.
Doses/concentration levels	0, 1000, 2000, 4000, or 8000 ppm.
Sex	40 male, 40 female per group.
Exposure period	6 hours/day.
Frequency of treatment	5 days/week for 13 weeks.
Control group and treatment	40 male, 40 female, exposed to filtered air only.
Post exposure observation period	Not applicable.
Statistical methods	Analysis of variance for body weights, food consumption, urinalysis, hematology, clinical chemistry, organ weights.
Test Conditions	Groups of 40 rats/sex /group (approx. 5 weeks age at study initiation) were exposed to various levels of 1,3-butadiene for 6 hrs/day, 5 days/week for 13 weeks. All animals were observed daily; individual body weights and food consumption were recorded weekly. Interim sacrifices of 10 rats/sex/group were performed after 2 and 6 weeks of exposure. Three urine samples were obtained from each animal during the 1-2 weeks prior to sacrifice. Blood samples were collected from all rats prior to the 2, 6, and 13 week sacrifices. Brain cholinesterase activity was measured using half the brain of 5 rats/sex/group at the 2 and 6-week sacrifices and all rats at the terminal sacrifice. Organ weights were recorded for the adrenals, brain, gonads, heart, kidneys, liver, lung, pituitary, spleen, and thyroid. Necropsies were performed and tissues preserved. Histopathologic examinations were performed on all control and high exposure (8000 ppm) tissues.
Results	
NOAEL (NOEL)	8000 ppm.
LOAEL (LOEL)	>8000 ppm.
Remarks	Increased salivation was observed in the females after 8 weeks exposure and decreased grooming (stained fur) in the males after 10 weeks. No other exposure-related conditions were observed. Male rats showed slight (non-statistically significant) reductions in body weight gains compared to the controls; female body weights at 1000 and 4000 ppm were statistically higher than the controls. Neuromuscular function tests using a modified rotating cone gave some random group differences, but were not considered exposure-related. There were no toxicologically significant differences in hematology, blood chemistry, brain cholinesterase measurements, or urine analysis. Organ weight and organ to brain weight ratios showed some scattered statistically significant differences among the groups but did not indicate any treatment-related effects.

	Microscopic examination of the tissues of the exposed rats showed a similar incidence and severity of histopathologic findings to the control group.
Conclusions (study author)	Rats exposed to butadiene gas at concentrations up to 8000 ppm showed no significant effects related to exposure.
Data Quality Reliabilities	Reliable without restrictions. Comparable to guideline study.
References	Crouch, C.N., Pullinger, D.H., and Gaunt, I.F. (1979) Inhalation Toxicity Studies With 1,3-butadiene - 2. 3 Month Toxicity Study in Rats. Am. Ind. Hyg. Assoc. J. 40:796-802.
Other Last changed	Robust Summary Prepared by ExxonMobil Biomedical Sciences, Inc. 18-Oct-99

Robust Summary - Group 1: High Butadiene C4

Developmental Toxicity/Teratogenicity

Test Substance	
Remarks	1,3-butadiene, CAS# 106-99-0 Purity 99.88%
Method	
Method/guideline followed	OECD 414.
Test type	Developmental toxicity (teratogenicity) study.
GLP	Yes.
Year	1987.
Species	Mouse.
Strain	CD-1 (Swiss).
Route of administration	Inhalation (gas).
Concentration levels	0, 40, 200, or 1000 ppm.
Sex	18-22 pregnant females per group.
Exposure period	Days 6-15 of gestation.
Frequency of treatment	6 hours/day.
Control group and treatment	Air-exposed only.
Duration of test	Females sacrificed on gestation day 18.
Statistical methods	Analysis of variance for body weights, number of resorptions, implants, live, dead or affected fetuses per litter. Significant differences among the groups were also analyzed by Duncan's multiple range test or arcsin transformation of the response proportion. Binary-response variables were between groups were compared using chi-square or Fisher's exact test.
Remarks for Test Conditions.	Female mice were mated to unexposed males and exposed from days 6-15 of gestation to 0, 40, 200, or 1000 ppm of the test substance. Analytical chamber concentrations were measured by on-line gas chromatography. Body weights were recorded on gestation days 0, 6, 11, 16, and 18. Maternal animals were observed daily for mortality, morbidity, and signs of toxicity and examined for gross tissue abnormalities at necropsy (day 18). The uterus and placenta was removed and weighed; the number of implantation sites, resorptions, live and dead fetuses were recorded. Live fetuses were weighed and subjected to external, visceral, and skeletal examinations. Approximately 50% of the fetal heads were sectioned and examined.
Results	
NOAEL maternal toxicity	40 ppm.
NOAEL developmental toxicity	40 ppm. There were decreases in maternal body weight gains in the 200 and 1000 ppm groups. Fetal weights were significantly reduced in both males and females at 200 and 1000 ppm; placenta weights were significantly reduced for corresponding male fetuses at 200 ppm and for both males and females at 1000 ppm. There were no significant differences in percent resorptions or malformations per litter, although there was an increase in fetal variations (supernumary ribs and reduced ossification of sternebrae) at 200 and 1000 ppm.
Conclusions	
(study author)	Developmental toxicity was observed in mice in the presence of maternal toxicity at 200 and 1000 ppm. A slight statistically significant decrease in male fetal weight (95% of control) was also observed, but the biological significance of this finding has been questioned.

Data Quality *Reliabilities*	Reliable without restrictions. Guideline study.
References	Morrissey, R.E., Schwetz, B.A., Hackett, P.L., Sikov, M.R., Hardin, B.D., McClanahan, B.J., Decker, J.R., and Mast, T.J. (1990). Overview of Reproductive and Developmental Toxicity Studies of 1,3-Butadiene in Rodents. Environ. Health Perspect. 86:79-84.
Other Las*t changed*	Robust Summary Prepared by ExxonMobil Biomedical Sciences, Inc. 20-Oct-99

Robust Summary - Group 1: High Butadiene C4

Developmental Toxicity/Teratogenicity

Test Substance	
Remarks	1,3-butadiene, CAS# 106-99-0 Purity 99.88%
Method	
Method/guideline followed	OECD 414.
Test type	Developmental toxicity (teratogenicity) study.
GLP	Yes.
Year	1987.
Species	Rat.
Strain	CD (Sprague-Dawley).
Route of administration	Inhalation (gas).
Concentration levels	0, 40, 200, or 1000 ppm.
Sex	24-28 pregnant females per group.
Exposure period	Days 6-15 of gestation.
Frequency of treatment	6 hours/day.
Control group and treatment	Air-exposed only.
Duration of test	Females sacrificed on gestation day 20.
Statistical methods	Analysis of variance for body weights, number of resorptions, implants, live, dead or affected fetuses per litter. Significant differences among the groups were also analyzed by Duncan's multiple range test or arcsin transformation of the response proportion. Binary-response variables between groups were compared using chi-square or Fisher's exact test.
Remarks for Test Conditions.	Female rats were mated to unexposed males and exposed from days 6-15 of gestation to 0, 40, 200, or 1000 ppm of the test substance. Analytical chamber concentrations were measured by on-line gas chromatography. Body weights were recorded on gestation days 0, 6, 11, 16, and 20. Maternal animals were observed daily for mortality, morbidity, and signs of toxicity and examined for gross tissue abnormalities at necropsy (day 20). The uterus and placenta was removed and weighed; the number of implantation sites, resorptions, live and dead fetuses were recorded. Live fetuses were weighed and subjected to external, visceral, and skeletal examinations. Approximately 50% of the fetal heads were sectioned and examined.
Results	
NOAEL maternal toxicity	200 ppm
NOAEL developmental	1000 ppm
toxicity	The only toxicity observed was decreased body weight gains in the dams at 1000 ppm. The percentage of pregnant animals and number of litters with live fetuses were unaffected by treatment. There were no significant differences among the groups for number of live fetuses per litter, percent resorptions or malformations per litter, placental or fetal body weights, or sex ratio.
Conclusions	
(study author)	There was no evidence of teratagenicity or adverse reproductive effects in any of the exposed groups.
Data Quality	
Reliabilities	Reliable without restrictions. Guideline study.

References	Morrissey, R.E., Schwetz, B.A., Hackett, P.L., Sikov, M.R., Hardin, B.D., McClanahan, B.J., Decker, J.R., and Mast, T.J. (1990). Overview of Reproductive and Developmental Toxicity Studies of 1,3-Butadiene in Rodents. Environ. Health Perspect. 86:79-84.
Other La*st changed*	Robust Summary Prepared by ExxonMobil Biomedical Sciences, Inc. 20-Oct-99

Robust Summary - Group 1: High Butadiene C4

Toxicity to Reproduction

Test Substance	
Remarks	1,3-butadiene, CAS# 106-99-0 Purity 99.88%
Method	
Method/guideline followed	Other.
Test type	Sperm-head morphology assay.
GLP	Yes.
Year	1987.
Species	Mouse.
Strain	B6C3F1.
Route of administration	Inhalation (gas).
Concentration levels	0, 200, 1000, and 5000 ppm.
Sex	20 males per group.
Exposure period	6 hours/day.
Frequency of treatment	5 days.
Control group and treatment	Air-exposed only.
Duration of test	Males sacrificed 5 weeks post-exposure.
Statistical methods	Normal and abnormal sperm heads were expressed as percentage of the total number of cells examined. These data were subjected to arcsin transformation and evaluated by analysis of variance. If significant, Duncan's multiple range test was used for intergroup differences. Dose response trends were determined by orthogonal contrast.
Remarks for Test Conditions.	The mice were observed twice daily and body weights recorded weekly. During the fifth week post-exposure the mice were sacrificed and examined for lesions of the reproductive tract and other gross abnormalities. Sperm was obtained from the cauda of the right epididymis. Slides were prepared, stained, and examined microscopically. The morphology of at least 500 sperm heads per mouse was categorized.
Results	
NOAEL	200 ppm
	The percentage of abnormal sperm heads increased with exposure concentration: 1.61% (0 ppm), 1.95% (200 ppm), 2.79% (1000 ppm), and 3.79% (5000 ppm). Only the values for the 1000 and 5000 ppm groups were significantly different from the control ($p < 0.05$). Only a single timepoint was examined, so the effect on all stages of spermatogenesis could not be determined.
Conclusions	
(Study author)	These results suggest that the test substance affected spermatogenesis in mice at 1000 and 5000 ppm, but the effect of this observation on other reproductive endpoints is not known.
Data Quality	
Reliabilities	Reliable with restrictions. Acceptable, well-documented publication which meets basic scientific principles.

References	Morrissey, R.E., Schwetz, B.A., Hackett, P.L., Sikov, M.R., Hardin, B.D., McClanahan, B.J., Decker, J.R., and Mast, T.J. (1990). Overview of Reproductive and Developmental Toxicity Studies of 1,3-Butadiene in Rodents. Environ. Health Perspect. 86:79-84.
Other La*st changed*	Robust Summaries Prepared by ExxonMobil Biomedical Sciences, Inc. 20-Oct-99

.**Robust Summary - Group 1: High Butadiene C4**

Toxicity to Reproduction

Test Substance	
Remarks	1,3-butadiene, CAS# 106-99-0 Purity 99.88%
Method	
Method/guideline followed	Other.
Test type	Rodent dominant lethal test.
GLP	Yes.
Year	1987.
Species	Mouse
Strain	CD-1 (Swiss).
Route of administration	Inhalation (gas).
Concentration levels	0, 200, 1000, and 5000 ppm.
Sex	20 males per group.
Exposure period	6 hours/day.
Frequency of treatment	5 days.
Control group and treatment	Air-exposed only.
Duration of test	8 weeks post-exposure.
Statistical methods	The number of implantation sites and intrauterine deaths per litter for each week were analyzed by analysis of variance. When appropriate, proportions of resorptions and dead or live fetuses per implant were subjected to arcsin transformation and evaluated by analysis of variance. If significant, Duncan's multiple range test was used for intergroup differences.
Remarks for Test Conditions.	After five days of exposure, the male mice were mated with unexposed females (two females per week for each male for 8 consecutive weeks). Females were removed from cohabitation after 7 days sacrificed 12 days later and the uterine contents examined. Observations included: the total number, position, and status of implantations; the numbers of early and late resorptions; and numbers of live and dead fetuses.
Results	Slight statistically significant effects were noted in the mated females for three endpoints during the first 2 weeks post-exposure: ratio of dead to total implants, percentage of females with $\geq$2 dead implants, and number of dead implants per pregnancy. However, these observations only occurred in the two lower exposure groups (except for increased number dead implants/pregnancy in the 5000 ppm group during week 1). There were no differences for number of pregnant females, implantations per litter, number of live fetuses, dead implantations per total implantations, or number of resorptions during weeks 1 and 2. There were no differences for any endpoint during weeks 3-8.
Conclusions	
(Study author)	The authors concluded that the results observed during the first two weeks are consistent with an adverse effect on more mature germ cells (spermatozoa and spermatids) however considering the lack of effects in the high exposure group the findings are not clear for a dose-dependent response.
Data Quality	
Reliabilities	Reliable with restrictions. Acceptable, well-documented publication which meets basic scientific principles.

References	Morrissey, R.E., Schwetz, B.A., Hackett, P.L., Sikov, M.R., Hardin, B.D., McClanahan, B.J., Decker, J.R., and Mast, T.J. (1990). Overview of Reproductive and Developmental Toxicity Studies of 1,3-Butadiene in Rodents. Environ. Health Perspect. 86:79-84.
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